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10/528,843	01/23/2006	Tatsuo Hoshino	21404 US C038435/0185948	2022
7590 Stephen M Haracz Bryan Cave 1290 Avenue of the Americas New York, NY 10104			EXAMINER CHOWDHURY, IQBAL HOSSAIN	
			ART UNIT 1652	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/528,843

Applicant(s)

HOSHINO ET AL.

Examiner

Iqbal H. Chowdhury, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 9-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 March 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 3/23/2005.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP03/10295.

Claims 1-11 are currently pending in the instant application.

Applicant's election with traverse of Group I, Claims 1-8, drawn to a process for producing actinol from ketoisophorone, which comprises contacting ketoisophorone with a recombinant microorganism or mutant thereof, wherein the microorganism comprises levodione reductase gene (cellular method) in the response filed on 3/2/2007 is acknowledged.

The traversal is on the ground(s) that the lack of unity established by the examiner between the Groups I to III, is improper. Applicants argue that there is no lack of unity. However, Examiner finds that lack of unity exists because the microorganism comprising a gene encoding a polypeptide of levodione reductase of Group III, and the method for producing actinol by using said microorganism comprising said gene encoding a polypeptide of levodione reductase of Group I or cell extract of recombinant microorganism of Group II, they all relate to polynucleotide encoding a polypeptide levodione reductase or polypeptide levodione reductase. However, this shared technical feature is not a "special technical feature" as defined by PCT Rule 13.2 as it does not define a contribution over the art. If there were no art regarding this special technical feature, then unity of invention is there but if prior art teaches that special technical feature, then lack of unity exists. As discussed previously, Yoshisumi et al. teach a DNA encoding a levodione reductase gene (Corynebacterium aquaticum lvr gene for levodione reductase, complete cds, GenBank Accession No. AB042262, created 10/12/2001) which is

known in the art. Thus, a DNA encoding a levodione reductase protein or use of that gene or protein in method also does not make contribution over the prior art.

Applicants further argue that the Special technical feature is a recombinant microorganism having the capability of reducing ketoisophorone to levodione and expressing the levodione reductase gene and Examiner's assertion is erroneous. This is not found persuasive because applicants asserted Special technical feature is not even a Shared feature of all claims as claims 3, 4 and 7-8 do not even require such a microorganism; therefore, this microorganism cannot be a Special technical feature in these claims.

As restriction is clearly permissible even among related inventions as defined in MPEP 808 and 35 U.S.C. 121 allows restriction of inventions, which are independent or distinct.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-8 are under consideration and are being examined herein.

Priority

Acknowledgement is made of applicants claim for foreign priority of EPO 02021605.7 filed on 9/27/2002.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3/23/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawing

The drawing of this application submitted on 3/23/2005 is being considered by the Examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 3, 5 and 7 recite the phrase "derived from microorganism". The metes and bounds of this phrase are not clear to the examiner. Literally, while the term "derive" means "to isolate from or obtain from a source", the above term could also mean, "to produce or obtain from another substance". Therefore, it is not clear to the examiner either from the specification or from the claims as to what applicants mean by the above phrase. It is not clear to the Examiner whether the gene "derived from microorganism" encompasses a single specific gene or it encompasses variants and mutants of any levodione reductase gene from any species or modified levodione reductase from any other source and labeled as "derived from microorganism". As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to mean that a gene "derived from microorganism" encompasses nucleic acid sequences, which are variants, and mutants of any levodione reductase gene. Examiner has given the same interpretation while considering the claims for all other rejections.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant

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regards as the invention. In the present instance, claims 1, 3, 5 and 7 recite the term "mutant thereof" in the context of *Corynebacterium aquaticum* AKU611 strain, which is unclear as to the scope of said strain that is encompassed. In another words, how many changes can be made to the microbial strain and still be a "mutant thereof"?

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 3, 5, and 7 recite "such as" renders the claim(s) indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Accordingly claims 2, 4, 6 and 8 are rejected as they dependent on claims 1, 3, 5 or 7.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claims 1, 3, 5 and 7, the phrase "e.g. or for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 2, 4, 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2, 4, 6 and 8 are indefinite with the recitation "preferably", which is unclear as to the scope of the claim. The phrase "preferably" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to a process for producing actinol from ketoisophorone comprising contacting ketoisophorone with a recombinant microorganism having ketoisophorone reductase activity comprising a levodione reductase gene encoding protein or cell free extract thereof or a mutant strains thereof, or cell-free extract from mutant strains thereof and isolating the resulting actinol from the reaction mixture. Claims 3, 5 and 7 are directed to a process for producing actinol from ketoisophorone comprising contacting ketoisophorone with a recombinant microorganism having levodione reductase activity comprising a ketoisophorone reductase gene encoding protein or cell free extract thereof or a mutant strains thereof, or cell-free extract from mutant strains thereof and isolating the resulting actinol from the reaction mixture (claim 3), or a process for producing actinol from ketoisophorone comprising contacting ketoisophorone with a recombinant microorganism comprising a levodione reductase gene encoding protein and a ketoisophorone reductase gene encoding protein or cell free extract thereof or a mutant strains thereof, or cell-free extract from mutant strains thereof and isolating the resulting actinol from the reaction mixture (claim 5) or a process for producing actinol from ketoisophorone comprising contacting ketoisophorone with purified levodione reductase protein and

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ketoisophorone reductase protein or mutant of said proteins and isolating the resulting actinol from the reaction mixture. Claims 2, 4, 6 and 8 recite the process, wherein the reaction is carried out at pH values, preferably from 5.0 to 8.0 and at a temperature range of 20 to 40°C and for 30 minutes to 48 hrs.

Thus, claims 1-8 are drawn to a process for producing actinol from ketoisophorone comprising contacting ketoisophorone with a recombinant microorganism or a cell free extract thereof or a mutant strains thereof or proteins purified therefrom, and isolating the resulting actinol from the reaction mixture. Claims are drawn to a process of using any microorganism expressing any levodione reductase or any ketoisophorone reductase including mutants or variants thereof whose structures are not fully described in the specification except that said levodione reductase gene is from *C. aquaticum*. No information, beyond the characterization of the microorganisms producing a levodione reductase from a strain of *C. aquaticum* or a ketoisophorone reductase from genera *Saccharomyces*, *Zygosaccharomyces* or *Candida*, having the activity of reducing ketoisophorone to levodione and levodione to actinol has been provided, which would indicate that applicants had possession of the method of using the genus of any levodione reductase enzymes or any ketoisophorone reductase enzymes produced by the microorganism for converting ketoisophorone to actinol. The specification does not contain any disclosure of the structure of all the mutants or variants of any levodione reductase enzyme from *C. aquaticum* and any ketoisophorone reductase from any microorganism that of microorganism producing the same within the scope of the claimed genus. The specification also does not contain any disclosure about any specific microorganism capable of reducing ketoisophorone to levodione or capable of reducing levodione to actinol within the scope of the claimed genus. The

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genus of microorganism or the polypeptides used is a large variable genus, which can have wide variety structures. Therefore, many structurally unrelated polypeptides and many microorganisms producing the same are encompassed within the scope of these claims. The specification discloses the structure of only a single representative species i.e., *C. aquaticum* AKU611 which is the source of said gene encoding levodione reductase enzyme used in the claimed method but no information about a specific source of ketoisophorone reductase enzyme or any specific microorganism used in the claimed method, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing actinol from ketoisophorone by using a *Saccharomyces cerevisiae* INVScI strain comprising a levodione reductase gene isolated from *Corynebacterium aquaticum* AKU611, does not reasonably provide enablement for 1) a process for producing actinol from ketoisophorone by using any microorganism comprising any levodione reductase gene from any source or any mutant strain comprising any mutant or any variant of any levodione reductase gene or any cell extract from any microorganism comprising any levodione reductase gene or any mutant strain comprising any mutant or any variant of any

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levodione reductase gene; 2) a process for producing actinol from ketoisophorone by using any microorganism comprising any ketoisophorone reductase gene from any source or any mutant strain comprising any mutant or any variant of any ketoisophorone reductase gene or any cell extract from any microorganism comprising any ketoisophorone reductase gene or any mutant strain comprising any mutant or any variant of any ketoisophorone reductase gene; 3) a process for producing actinol from ketoisophorone by using any microorganism comprising any levodione reductase gene and ketoisophorone reductase gene from any source or any mutant strain comprising any mutant or any variant of said reductase genes or any cell extract from any microorganism comprising any levodione reductase gene and ketoisophorone reductase gene or any mutant strain comprising any mutant or any variant of said reductase genes; and 4) a process for producing actinol from ketoisophorone by using any levodione reductase purified protein and any ketoisophorone reductase protein from any source or any mutant thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1 and 2 are so broad as to encompass a process for producing actinol from ketoisophorone by using a microorganism having ketoisophorone reductase activity comprising any levodione reductase gene for reducing levodione to actinol or any mutant strain thereof comprising any mutant or any variant of any levodione reductase gene or a cell extract from said microorganism (genus) comprising any levodione reductase gene, mutant or variant said levodione reductase gene. Claims 3-4 are also broad in the context of a process for producing actinol from ketoisophorone by using any microorganism having levodione reductase activity comprising any ketoisophorone reductase gene or any mutant strain thereof comprising any

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mutant or any variant of any ketoisophorone reductase gene or a cell extract from said microorganism comprising any ketoisophorone reductase, or mutants or variants of said ketoisophorone, wherein the process of reaction that is carried out at pH values, preferably from 5.0 to 8.0 and at a temperature range of 20 to 40°C and for 30 minutes to 48 hrs. Claims 5-8 are drawn to a process for producing actinol from ketoisophorone or a mutant strain thereof, expresses both ketoisophorone reductase gene and levodione reductase gene, or using purified polypeptide of levodione reductase and ketoisophorone reductase, and isolating the produced actinol from the reaction mixture, wherein the reaction is carried out at pH values of from 4.0 to 9.0, preferably from 5.0 to 8.0, and at a temperature in the range of from 10 to 50°C, preferably from 20 to 40°C, and for 5 minutes to 72 hours, preferably for 15 minutes to 24 hours.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to a process of using extremely large number of levodione reductase genes and proteins, and ketoisophorone reductase genes and proteins broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the methods comprising nucleotide and encoded amino acid sequence of only one levodione reductase gene and one ketoisophorone reductase gene.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The scope of the claims is also not commensurate with the enablement provided by the disclosure with regard to a process of using extremely large number of microorganisms having levodione reductase activity capable of reducing levodione to actinol or ketoisophorone reductase activity capable of reducing ketoisophorone to levodione broadly encompassed by the claims.

While methods of using microorganism having levodione reductase activity and ketoisophorone reductase activity in vitro are well known in the art, selecting a microorganism having optimum activity of said enzymes are not routine. Since, microorganism having genes encoding proteins are always mutating spontaneously resulting in a wide variety of activity (from no activity to high activity). Knowledge of single species of microorganism comprising said genes encoding proteins is unlikely to be provide any guidance for using any other types of microorganism. However, in this case the disclosure is limited to *Saccharomyces cerevisiae* INVScI strain comprising said genes.

The specification does not support the broad scope of the claims which encompass a process for producing actinol from ketoisophorone by using any microorganism comprising any

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levodione reductase gene or any ketoisophorone reductase gene or mutant strain thereof comprising any mutant or any variant of any levodione reductase gene or/and ketoisophorone reductase gene or a cell extract from said microorganism comprising any levodione reductase gene or/and any ketoisophorone reductase gene, mutant or variant said reductase genes because the specification does not establish: (A) regions of the protein structure which may be modified without affecting levodione reductase or ketoisophorone reductase activity; (B) the general tolerance of levodione reductase or ketoisophorone reductase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any levodione reductase and any ketoisophorone reductase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a process for producing actinol from ketoisophorone by using a microorganism having ketoisophorone reductase activity comprising any levodione reductase gene for reducing levodione to actinol or any mutant strain thereof comprising any mutant or any variant of any levodione reductase gene or a cell extract from said microorganism comprising any levodione reductase gene, mutant or variant of said levodione reductase gene used in the method or a microorganism having levodione activity comprising any ketoisophorone reductase gene or using any levodione reductase protein or using any ketoisophorone reductase protein or using any levodione reductase and ketoisophorone reductase protein simultaneously. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166

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USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a process for producing actinol from ketoisophorone by using a microorganism comprising any levodione reductase gene and any ketoisophorone reductase having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 3, 5 and 7 are drawn method of using novel microorganisms. Since the microorganisms are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The recited microorganisms have not been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. 112 may be satisfied by a deposit of the microorganisms. The specification does not disclose a repeatable process to obtain the microorganisms and it is not apparent if the DNA sequences required for construction of the vectors in such microorganisms are readily available to the public. Accordingly, it is deemed that a deposit of these microorganisms should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited some of the organisms but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of

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record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
2. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808;
3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
4. the deposit will be replaced if it should ever become unavailable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Wada et al.
(Production of a doubly chiral compound, (4R,6R)-4-hydroxy-2,2,6-trimethylcyclohexanone, by

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two-step enzymatic asymmetric reduction, Appl Environ Microbiol. 2003 Feb;69(2):933-7, see IDS). Claims 1-6 are drawn to a process for producing actinol from ketoisophorone by using a microorganism having ketoisophorone activity comprising any levodione reductase gene or mutant strain thereof comprising any mutant or any variant of any levodione reductase gene or a cell extract from said microorganisms comprising any levodione reductase gene, mutant or variant said levodione reductase gene or using any microorganism having levodione reductase activity comprising any ketoisophorone reductase gene or mutants or variants of said gene, mutant strain thereof or cell extract thereof or a microorganism expressing both ketoisophorone reductase gene and levodione reductase gene, and isolating the produced actinol from the reaction mixture, wherein the reaction is carried out at pH values of from 4.0 to 9.0, preferably from 5.0 to 8.0, and at a temperature in the range of from 10 to 50°C, preferably from 20 to 40°C, and for 5 minutes to 72 hours, preferably for 15 minutes to 24 hours.

Wada et al. teach a method for producing actinol from ketoisophorone (KIP) by using cell extract of *E. coli* transformed with the *S. cerevisiae* 04E2 gene encoding a protein having ketoisophorone reductase activity and the levodione reductase gene from *Corynebacterium aquaticum*, followed by expression of said genes encoding proteins, wherein said *E. coli* converts ketoisophorone to actinol. Wada et al. also teach that said microbial cell extract capable of producing actinol from levodione. Wada et al. further teach isolating actinol from the mixture by organic solvent ethyl acetate and determined by gas chromatography followed by quantitatively determined of the concentration. Wada et al. furthermore teach that the reaction assay is performed at pH 7-8, temperature 25-37°C for 30 min for the production of levodione or actinol from ketoisophorone. Therefore, Wada et al. anticipate claims 1-6 of instant application.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by EP0982406 A2 (microbial production of actinol, publication 1/3/2000, see IDS). Claim 1-2 are drawn to a process for producing actinol from ketoisophorone by using a microorganism having ketoisophorone activity comprising any levodione reductase gene or mutant strain thereof comprising any mutant or any variant of any levodione reductase gene or a cell extract from said microorganisms comprising any levodione reductase gene, mutant or variant said levodione reductase gene, and isolating the produced actinol from the reaction mixture, wherein the reaction is carried out at pH values of from 4.0 to 9.0, preferably from 5.0 to 8.0, and at a temperature in the range of from 10 to 50°C, preferably from 20 to 40°C, and for 5 minutes to 72 hours, preferably for 15 minutes to 24 hours.

EP0982406 teaches a process for microbial production of actinol from ketoisophorone (KIP) through levodione. The conversion of KIP to actinol through levodione is performed by the enzyme levodione reductase inherently present in the microorganism either constitutive expression or transformed by the said levodione reductase gene from *C. aquaticum*. Therefore, EP0982406 discloses a process for producing actinol from KIP. EP0982406 also discloses the microorganisms which can convert KIP/levodione to actinol such as *Cellulomonas*, *Corynebacterium*, *Planococcus* and *arthrobacter* including *Cellulomonas* sp. AKU672, *Corynebacterium aquaticum* AKU610 and *Corynebacterium aquaticum* AKU611, *Planococcus okeanokoites* AKU152 and *Arthrobacter sulfurous* AKU635 and isolating the products and recovering and quantitative concentration determination. EP0982406 further discloses the

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process performed at pH range 4-9, temperature 20-50°C for 10 min to 80 hrs. Therefore, EP0982406 anticipates claims 1-2 of instant application.

Claims 3-4 are rejected under 35 U.S.C. 102(e) as being anticipated by Kataoka et al. (WO 03/070924 A1, publication 8/28/2003, see IDS). Claim 3-4 are drawn to a process for producing actinol from ketoisophorone by using a microorganism having levodione reductase activity comprising any ketoisophorone reductase or enone reductase gene or mutant strain thereof comprising any mutant or any variant of any ketoisophorone reductase or enone reductase gene or a cell extract from said microorganisms comprising any ketoisophorone reductase or enone reductase gene, and isolating the produced actinol from the reaction mixture, wherein the reaction is carried out at pH values of from 4.0 to 9.0, preferably from 5.0 to 8.0, and at a temperature in the range of from 10 to 50°C, preferably from 20 to 40°C, and for 5 minutes to 72 hours, preferably for 15 minutes to 24 hours.

Kataoka et al. teach a process for producing levodione from ketoisophorone by using a gene encoding protein of enone reductase in a microorganism of *Candida macedoniensis*, a yeast strain. Because, said microorganism comprises natural levodione reductase gene, therefore, this microorganism inherently would produce actinol from substrate levodione, which is produced by the enone reductase gene. Kataoka et al. also teach that the reaction is carried out at temperature optima of 55-60°C, pH optima 4.5-8.5 for 24 hr. Therefore, Kataoka et al. anticipates Claims 3-4 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-6 rejected under 35 U.S.C. 103(a) as being unpatentable over EP0982406 A2 (microbial production of actinol, publication 1/3/2000, see IDS) in view of Kataoka et al. (WO 03/070924, publication 8/23/2003). Instant claims are drawn to a process for producing actinol from ketoisophorone by using a microorganism of genus *Saccharomyces*, *Zygosaccharomyces* or *Candida* comprising any levodione reductase gene from *C. aquaticum* or mutant strain thereof comprising any mutant or any variant of any levodione reductase gene or a cell extract from said microorganisms comprising any levodione reductase gene, mutant or variant said levodione reductase gene or using any microorganism comprising any ketoisophorone reductase gene or mutants or variants of said gene, mutant strain thereof or cell extract thereof used in the method.

EP0982406 teaches a process for microbial production of actinol from ketoisophorone (KIP) through levodione. The conversion of KIP to actinol through levodione is performed by

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the enzyme levodione reductase inherently present in the microorganism either constitutive expression or transformed by the said levodione reductase gene. Therefore, EP0982406 discloses a process for producing actinol from KIP. EP0982406 also discloses the microorganisms which can convert KIP/levodione to actinol such as *Cellulomonas*, *Corynebacterium*, *Planococcus* and *arthrobacter* including *Cellulomonas* sp. AKU672, *Corynebacterium aquaticum* AKU610 and *Corynebacterium aquaticum* AKU611, *Planococcus okeanokoites* AKU152 and *Arthrobacter sulfurous* AKU635 and isolating the products and recovering and quantitative concentration determination. EP0982406 further discloses the process performed at pH range 4-9, temperature 20-50°C for 10 min to 80 hrs. EP0982406 does not teach use of ketoisophorone reductase, an enzyme, which reduces ketoisophorone to levodione.

Kataoka et al. teach a process for producing levodione from ketoisophorone by using a gene encoding protein of enone reductase in a microorganism of *Candida macedoniensis*, a yeast strain.

By combining the teachings of EP and Kataoka et al., it would have been obvious to one of ordinary skill in the art at the time of the invention was made to make a transform yeast host cell expressing levodione reductase gene of EP0982406 and enone reductase of Kataoka for producing actinol from ketoisophorone as taught by EP0982406.

One of ordinary skill in the art would have been motivated to use a microorganism expressing both genes for enhanced production of actinol from ketoisophorone, since actinol is used to synthesis make carotenoids, which has wide industrial application.

One of ordinary skill in the art would have a reasonable expectation of success because EP0982406 could successfully convert ketoisophorone to actinol.

Therefore, claims 5-6 would have been *prima facie* obvious to use of ordinary skill in the art.

Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP0982406 A2 (microbial production of actinol, publication 1/3/2000, see IDS) as applied to claims 1-6 above, and further in view of Wada et al. (Purification and characterization of monovalent cation-activated levodione reductase from *Corynebacterium aquaticum* M-13. Appl Environ Microbiol. 1999 Oct;65(10):4399-403, see IDS). Instant claims are drawn to a process for producing actinol from ketoisophorone by using purified ketoisophorone reductase and levodione reductase proteins, and isolating the produced actinol from the reaction mixture, wherein the reaction is carried out at pH values of from 4.0 to 9.0, preferably from 5.0 to 8.0, and at a temperature in the range of from 10 to 50°C, preferably from 20 to 40°C, and for 5 minutes to 72 hours, preferably for 15 minutes to 24 hours.

EP0982406 teaches a process for microbial production of actinol from ketoisophorone (KIP) through levodione. The conversion of KIP to actinol through levodione is performed by the enzyme levodione reductase inherently present in the microorganism either constitutive expression or transformed by the said levodione reductase gene. Therefore, EP0982406 discloses a process for producing actinol from KIP. EP0982406 also discloses the microorganisms which can convert KIP/levodione to actinol such as *Cellulomonas*, *Corynebacterium*, *Planococcus* and *arthrobacter* including *Cellulomonas* sp. AKU672, *Corynebacterium aquaticum* AKU610 and *Corynebacterium aquaticum* AKU611, *Planococcus*

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okeanokoites AKU152 and *Arthrobacter sulfurous* AKU635 and isolating the products and recovering and quantitative concentration determination. EP0982406 further discloses the process performed at pH range 4-9, temperature 20-50°C for 10 min to 80 hrs. EP0982406 does not teach use of use of purified said proteins in the method of the claims.

Wada et al. (1999) teach a process of producing actinol from levodione by using purified enzyme of levodione reductase from *C. aquaticum*.

By combining the teachings of EP and Wada et al., it would have been obvious to one of ordinary skill in the art at the time of the invention was made to purify the levodione reductase and ketoisophorone reductase protein of EP by using the method of Wada et al. (1999) and use the method of EP for producing actinol from ketoisophorone.

One of ordinary skill in the art would have been motivated to use purified proteins in place of crude extracts in view of its superior catalytic activity.

One of ordinary skill in the art would have a reasonable expectation of success because Wada et al. could successfully convert levodione to actinol by using purified levodione reductase protein.

Therefore, claims 7-8 would have been *prima facie* obvious to use of ordinary skill in the art.

Conclusion

Status of the claims:

Claims 1-11 are pending.

Claims 9-11 are withdrawn.

Claims 1-8 are rejected.

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No claim is in condition for allowance.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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